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(c) identifying a cell of the population of plant cells having a mutation located between the first and second fragments of the target gene.

REMARKS

Claims 1 and 16 have been amended to clarify the fact that the DNA sequence of the target gene must be known and that the trait is imparted to the plant cell or a regenerated plant instead of in the gene. Support for these amendments can be found throughout the Specification and in particular at pages 3 (lines 26-29), 4 (lines 9-10) and 6 (lines 12-13).

Claims 1-4 and 8-27 are under Final Rejection. The three (3) outstanding rejections are summarized below:

1. Scope of enablement: Claims 1-4 and 8-27 have been rejected under 35 USC 112, first paragraph;

2. Novelty: Claims 1 and 16 have been rejected under 35 USC 102(b) as being anticipated by Svab *et al* 1990; and

3. Obviousness: Claims 1-4 and 8-27 have been rejected as being unpatentable over Kmiec '181 in view of Dunder *et al* and in view of Applicants admissions.

The Applicants will respond to the 112 and 103 rejections together as there appears to be an internal inconsistency between these two rejections. The 102 rejection will be discussed separately.

102 Rejection

Claims 1 and 16 have been rejected under 35 USC 102(b) as being anticipated by Svab *et al* 1990. this rejection is respectfully traversed.

The Examiner has maintained this rejection based on the Applicants use of the term "recombinagenic oligonucleobase" and the fact that Svab *et al* describe a plant chloroplast transformation undergoing an homologous recombination event. It is well known that an applicant for a patent can be his own lexicographer. Claim terms are also read in view of the

definitions of those terms appearing in the Specification. In the present application "recombinagenic oligonucleobase" is defined on page 4 of the Specification as follows:

> The term "recombinagenic oligonucleobase" is used herein to denote the molecules that can be used in the present invention. Recombinagenic oligonucleobases include MDON, non-nucleotide containing molecules taught in Kmiec II and the molecules taught in the above noted commonly assigned patent applications.

The Specification, on page 1, paragraph 1, specifically distinguishes the present invention from the recombinant DNA technology where whole transgenes are inserted into plants to genetically alter them. In contrast, the present invention allows the skilled person to make a specific alteration of a specific pre-existing gene of a plant. The gene can be a native gene or a transgene. The invention utilizes duplex oligonucleotides having a mixture of RNA-like nucleotides and DNA-like nucleotides to effect the alteration that are referred to as 'mixed oligonucleotides' or MDON. These definitions and descriptions in the Specification clearly indicate that the term "recombinagenic oligonucleobase" that appears in Claims 1 and 16 does not read on, encompass or contemplate transformation with transgenes.

For the reasons given above Claims 1 and 16 do not read on the prior art relating to transgenes (Svab *et al* 1990). Withdrawal of this rejection is respectfully requested.

112 and 103 Rejections

Claims 1-4 and 8-27 have been rejected under 35 USC 112, first paragraph regarding the scope of enablement and under 35 USC 103 as being unpatentable over Kmiec '181 in view of Dunder *et al* and in view of the Applicants' admissions. Because of the inconsistency or "Catch-22" nature of these rejections the Applicants will discuss them together.

Claims 1 and 16 have been amended to specify that the target gene sequence must be known and to form the antecedent basis for the term "the target sequence" appearing in the claim. This limitation was already inherently in these two claims as evidenced by the term

"target gene" and the requirement that there be an homologous region and an heterologous region in the recombinagenic oligonucleobase. These claims are now clearer.

With regard to the scope of enablement argument made by the Examiner, the Applicants point to the detailed teachings in the specification. First, the mutation made by the presently claimed methods require that the target gene be known. This is needed for making the homologous regions and heterologous regions in the recombinagenic oligonucleobase (hereinafter "RO"). There are at least two different ways to obtain the desired trait in the mutant plant cell and plant regenerated therefrom. One is to change one or more amino acids in the gene product protein by mutating (changing) the DNA accordingly. This aspect of the invention requires that the specific mutation be known such as the examples given in the Specification relating to the AHAS/ALS gene (p. 12-13), the psbA gene (p. 13), the DHDPS gene (p. 13), the threonine dehydratase gene (p. 13), the S14/rp39 ribosomal protein gene (p. 13) and the ETR-1 ethylene receptor gene (p.18-19). All of the above identified genes have known mutations that produce a desirable trait or phenotype that is seen with one or more amino acid substitutions. These amino acid substitutions are made according to the present invention with the RO. Another way to obtain the desired trait is to knockout a known gene by mutating it to insert a stop codon, a frame shift or an interruption with the promoter. Examples of these embodiments are listed in the Specification and include knocking out the chs gene, the Lat52 gene, or the PAL gene to produce male sterile plants, the acid invertase gene and the UDP-glucose pyrophosphorylase genes to inhibit cold sweetening in potatoes, the PPO gene to inhibit browning, the O-methyltransferase gene to produce the brown mid-ribmutation in maize and sorghum and others. The present method is also useful in producing mutated plants having specific gene knockouts in order to study the functions in plants of the knocked out genes.

It can be readily seen that the present claims are not overly broad regarding scope of enablement. The presently claimed process can be used with a high degree of certainty once the gene sequence of a plant is known. To limit the Applicants only to claims that specify mutations

to specific regions of known genes would be unfair and frustrate the purpose of the United States Patent Laws.

Like most, if not all inventions, the presently claimed methods involve old elements that have been assembled in a novel and unobvious manner. As mentioned in the prior responses and the Beetham and Metz Declarations, the present RO are small single stranded molecules with short regions of secondary structure making these molecules fragile. The short regions of secondary structure, however, are critical to the function/activity of the RO. This is in stark contrast to the prior art relating to biolistics transformation where extremely large pieces of DNA that contain whole coding sequences and regulatory sequences that are typically plasmids of several thousand paired nucleotides. The effects of the harsh chemical (salt) and physical (shear) conditions seen in the prior art DNA biolistic transformation on the fragile RO was unknown at the time of the present invention. The question being asked at the time that the present invention was made was, "Will it work?" and the answer was, "We don't know!" The present Applicants confirmed that the biolistics process did indeed work as described in the present Specification in particular in the section titled "BIOLISTIC WORKING EXAMPLES."

The present claims are directed to a method of making a localized mutation to a known DNA sequence within a plant cell. The known DNA sequence can be a native gene or a transgene present in the plant. Because the DNA sequence is known, a RO can be prepared that has the requisite homologous and heterologous regions required by the claims. The RO is then adhered to a particle and the particle is introduced into the plant cell by a biolistic process. The introduced RO then performs its function and makes the mutation resulting in the desired trait in the plant cell (and the whole plant regenerated therefrom). The desired mutated cell is then identified and used to take advantage of the desirable new trait.

From the above it is clear that the present claims are commensurate in scope with the invention that was made and that the Specification complies with all of the requirement of 35 USC 112. It is also clear that the present claims are not obvious over the Kmiec '181 reference in view of Dunder *et al* and in view of the Applicants' admissions. The fragile nature of the RO,

the harsh chemical and physical conditions used in the prior art biolistics TRANSFORMATION art with large macromolecules and total lack of expectation of success found in the prior art lead only to a conclusion of nonobviousness. Withdrawal of the 112 and 103 rejections is respectfully solicited.

The Applicants believe that Claims 1-4 and 8-27 are in condition for allowance.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this SUBMISSION OF AMENDMENT UNDER 37 C.F.R. § 1.116 is being facsimile transmitted to the U.S. Patent and Trademark Office this 11th day of October 2002.

Signed: Elaine E. Calimquim

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The specification is changed as follows:

On page 7, line 12, please insert --(now US Patent 6,004,804),--before the word "and" and insert --(now US Patent 6,010,907),-- before the word "disclose".

Commonly assigned U.S. patent application Serial No. 09/078,063, filed May 12, 1998, now US Patent 6,004,804 and Serial No. 09/078,064, filed May 12, 1998, now US Patent 6,010,907, disclose a type of duplex recombinagenic oligonucleobase in which a strand has a sequence that is identical to that of the target gene and only the sequence of the "complementary" strand contains a heterologous region. This configuration results in one or more mismatched bases or a "heteroduplex" structure. The heterologous region of the heteroduplex recombinagenic oligonucleobases that are useful in the present invention is located in the strand that contains the deoxynucleotides. In one embodiment, the heterologous region is located on the strand that contains the 5' terminal nucleotide.

IN THE CLAIMS:

Claims 1 and 16 are amended as follows:

1. A method of making a localized mutation in a plant cell to a target gene having a known sequence causing a desired trait in [a target gene in a] the plant cell comprising the steps of:

(a) adhering to a particle a recombinagenic oligonucleobase, which contains a first homologous region which has a sequence identical to the sequence of at least 6 base pairs of a first fragment of the target gene and a second homologous region which has a sequence identical to the sequence of at least 6 base pairs of a second fragment of the target gene, and an

intervening region which contains at least 1 nucleobase heterologous to the target gene, which intervening region connects the first homologous region and the second homologous region;

(b) introducing the particle into a cell of a population of plant cells;

(c) identifying a cell of the population [cell] of plant cells having a mutation located between the first and second fragments of the target gene.

16. A method of making a localized mutation in a plant cell to a target gene having a known sequence causing a desired trait in [a target gene in a] the plant cell having a cell wall comprising the steps of:

(a) perforating the cell walls of a population of plant cells;

(b) introducing a recombinagenic oligonucleobase, which contains a first homologous region which has a sequence identical to the sequence of at least 6 base pairs of a first fragment of the target gene and a second homologous region which has a sequence identical to the sequence of at least 6 base pairs of a second fragment of the target gene, and an intervening region which contains at least 1 nucleobase heterologous to the target gene, which intervening region connects the first homologous region and the second homologous region;

(c) identifying a cell of the population of plant cells having a mutation located between the first and second fragments of the target gene.